Basics of Stem Cell Transplant

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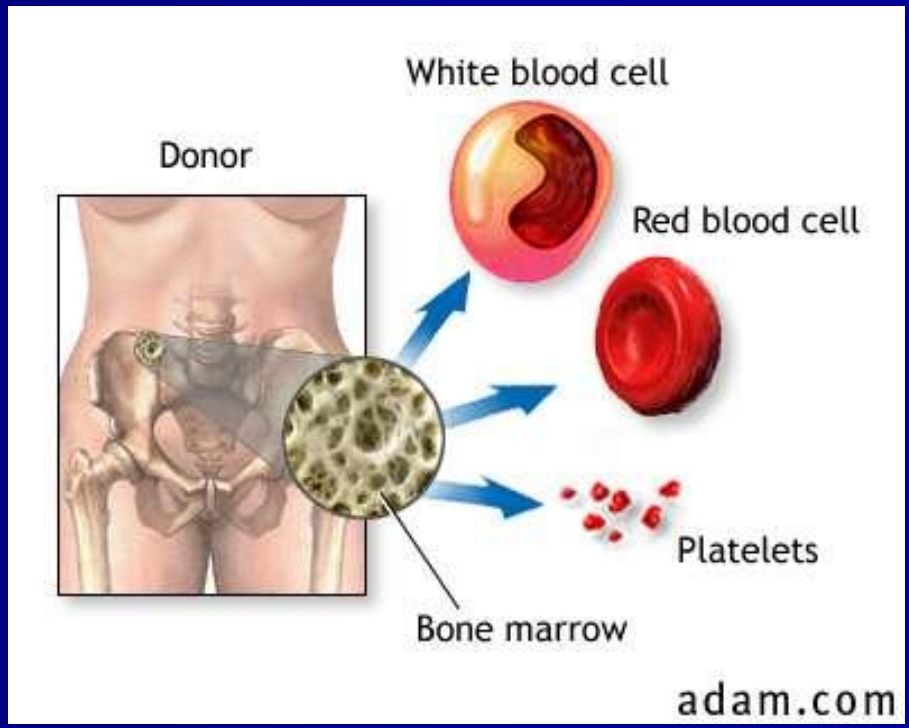


Background

- Hematopoietic stem cell transplantation
  - Intravenous infusion of autologous or allogeneic stem cells
    - Collected from bone marrow, peripheral blood or umbilical cord blood
  - Re-establish hematopoietic function in patients with damaged/defective bone marrow or immune systems
  - Potentially curative for a wide variety of disorders

Background

- First successful transplants—late 1960s
- 30,000-40,000 transplants performed yearly worldwide
- >20,000 patients have survived >5 years

Tranplant

- Patient's bone marrow stem cells are replaced with healthy cells
- Existing bone marrow and abnormal leukocytes killed
- Chemotherapy and radiation
- Next bone marrow containing healthy stem cells re-infused

Graft Sources

- Allogeneic: from another person
- Syngeneic: from an identical twin
- Autologous: from the patient

- Choice of graft is based on disease type, patient condition, donor compatibility and health

Graft Sources

- Autologous Transplant
  - No evidence of disease in the blood or bone marrow
  - Transplant related mortality (TRM) lowest with autos (<5%)
  - Relapse rates are higher depending on the disease
  - Absence of graft versus tumor effects

Graft Sources

- Allogeneic Transplants
  - High TRM (30-50%)
  - Lower relapse rates due to graft versus tumor effect.
  - Graft versus host disease.
- Matched Related Donor (siblings)
  - 25% chance a sibling will be a match
  - The more siblings a patient has the better chance for a match

Graft Sources

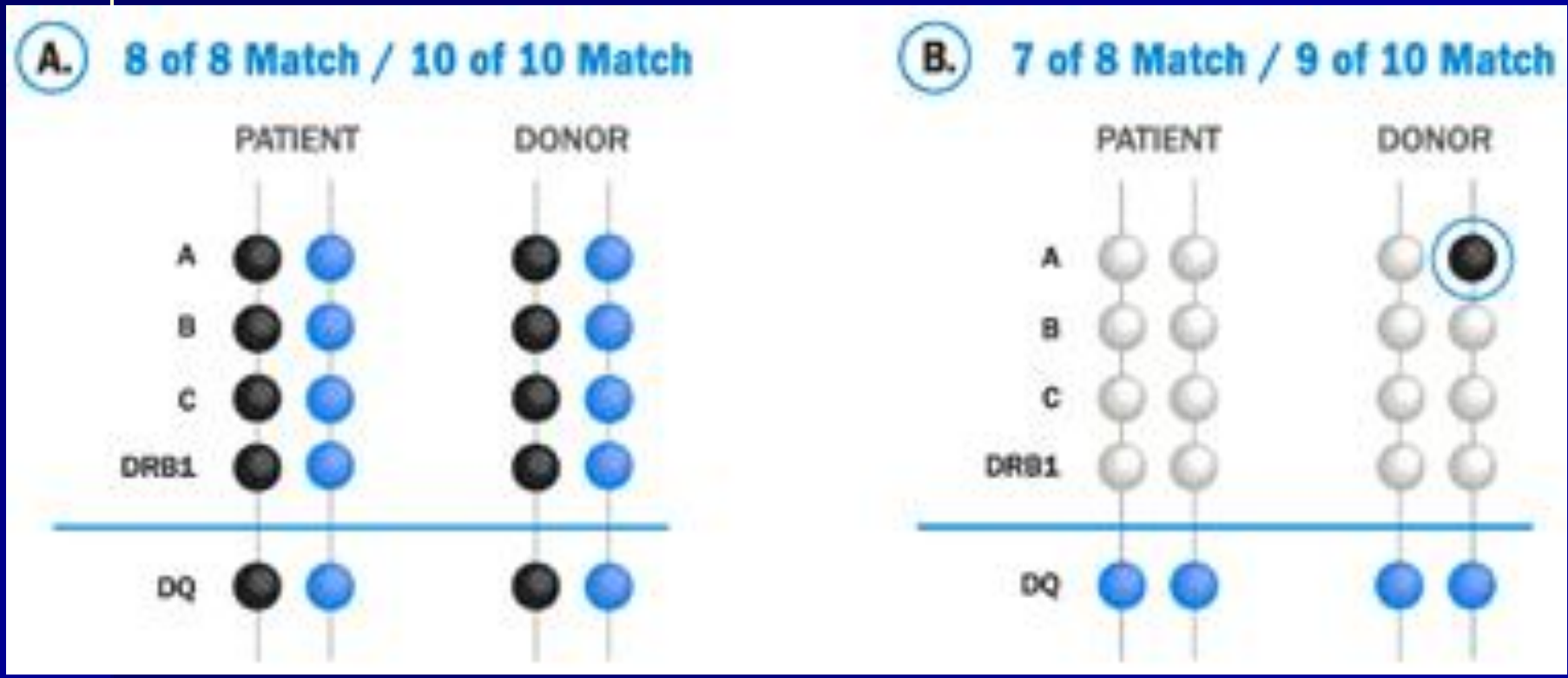
- Alternative Donors
  - Matched Unrelated Donors (MUD)
    - Severe GVHD
    - Higher TRM
  - Haploidentical Donors
    - From parent, child or sibling
    - Must have many stem cells to overcome risk of graft rejection
    - Increased risk of GVHD

HLA Typing

- HLA typing became feasible in 1960s
- Linked on chromosome 6
- Inherited as haplotypes
- 1 in 4 chance a sibling will be identical

HLA Matching

- There are 6 HLA markers that are matched.
- For a successful transplant, at least 4 of these 6 markers must match.
- HLA-A, HLA-B, HLA-C, HLA-DR, HLA-DQ, HLA-DP


A.
8 of 8 Match / 10 of 10 Match
PATIENT
DONOR
A
B
C
DRB1
DQ
B.
7 of 8 Match / 9 of 10 Match
PATIENT
DONOR
A
B
C
DRB1
DQ

Haploidentical Transplants

- A haploid-identical match is when the donor is a parent and the genetic match is at least half identical to the recipient.
- Parent, sibling or child
- High rate of engraftment failure
- GVHD

Indications Autologous Transplant

- Multiple myeloma
- NHL
- Hodgkin's disease
- AML
- Neuroblastoma
- Ovarian cancer
- Germ-cell tumors
- Autoimmune disorders
- Amyloidosis

Indications for Allogeneic Transplant

- AML
- ALL
- CML
- MDS
- MPD
- NHL
- Hodgkin's Disease
- CLL
- Multiple myeloma
- Juvenile CML
- Aplastic anemia
- PNH
- Fanconi's anemia
- Blackfan-Diamond
- Thalessemia major
- Sickle cell anemia
- SCID
- Wiskott-Aldrich
- Inborn errors of metabolism

Hematopoietic Progenitor Cell Sources

- Bone Marrow
- PBSC (peripheral blood stem cells)
- Umbilical Cord

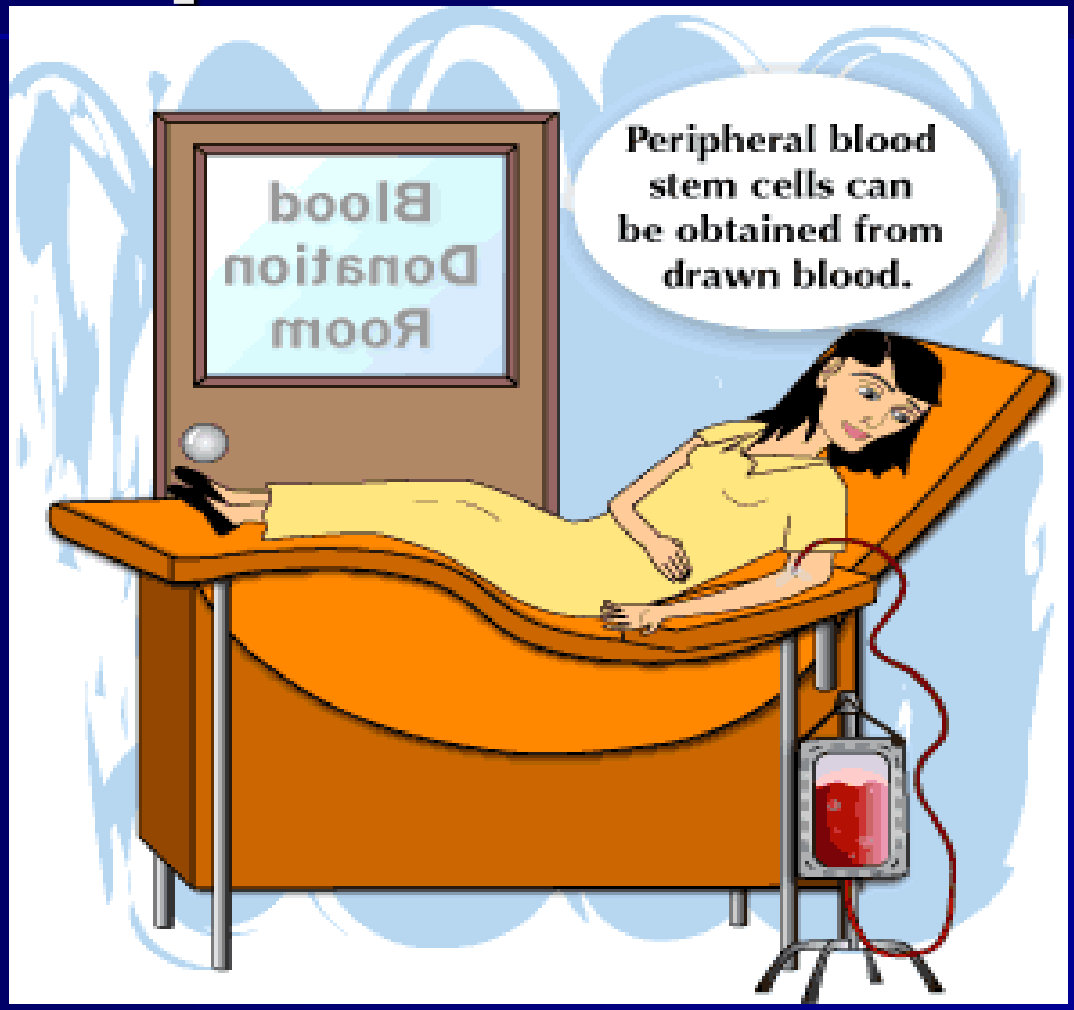
Peripheral blood stem cells

- Autologous transplants rely almost exclusively on PBSC rather than marrow due to:
- Easier collection of cells
- More rapid hematopoietic recovery
- Decreased costs

PBSC

- Most blood stem cells reside in the bone marrow and a small number are present in the bloodstream
- Multipotent peripheral blood stem cells
- Can be obtained from drawn blood
- PBSCs are easier to collect than bone marrow stem cells

Adult Stem Cell Transplant



Umbilical Cord Blood

- Physicians may consider umbilical cord blood a good choice particularly for patients who need an unrelated donor and have an uncommon HLA type or are in urgent need of a transplant.
- HLA mismatch is better tolerated – even with haploidentical donors
- Available more quickly than marrow or PBSC unrelated donors
- Reduced incidence and severity of GVHD

Umbilical Cord Blood

- 1st UCB transplant 16 years ago
  - Child with Fanconi's anemia
- Cell dose is given per recipient weight
  - Lower patient weights the high the cell dose
  - 2 x 10^7 nucleated cells/kg
  - 1.7 x 10^7 CD 34+ cells/kg
- 4/6 match UCB with sufficient cells has a similar outcome to a matched or one antigen mismatched matched unrelated donor (MUD).

Umbilical Cord Blood

- Lower GVHD
- TRM not different than MUD
- Can be used with myeloablative or nonmyeloablative conditioning (on a clinical trial)

Transplant Process (5 steps)

(1) Conditioning,
(2) Stem cell infusion,
(3) Neutropenic phase,
(4) Engraftment phase
(5) Post-engraftment period.

Conditioning Phase

- The conditioning period typically lasts 7-10 days.
- The purposes are (by delivery of chemotherapy and/or radiation)
  - to eliminate malignancy
  - to provide immune suppression to prevent rejection of new stem cells
  - create space for the new cells
- Radiation and chemotherapy agents differ in their abilities to achieve these goals.

Collection of Stem Cells

- Bone Marrow Harvest
  - General anesthesia
  - Equivalent of 50-100 bone marrow biopsies
  - Used much less often
  - 2 deaths in 8000 collections

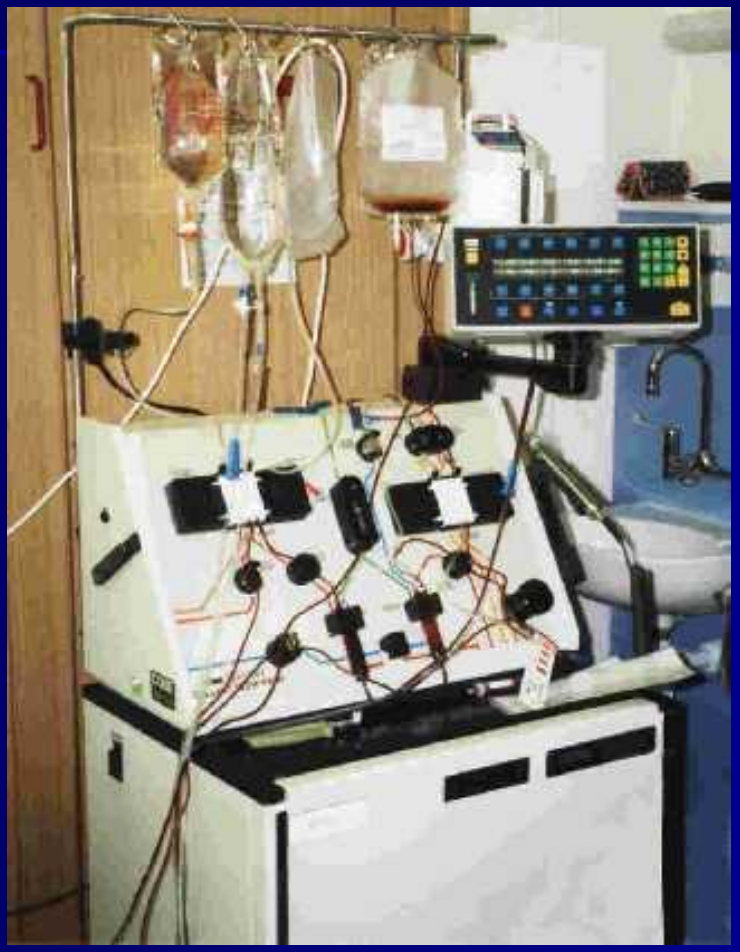
Collection of Stem Cells

- Stem Cell Collection (mobilization)
  - Stem cells circulate in the blood
  - Identified by CD34+ by flow cytometry
  - Stem cells are collected through an apheresis catheter
  - More cells are collected
  - Higher chronic GVHD than bone marrow harvest
  - More rapid marrow recovery

Collection of Stem Cells

- Harvesting stem cells from the blood stream is accomplished by a process called apheresis.
- The patient is connected to a cell separation machine via a needle in each arm. Blood is taken from one arm, circulated through the machine to remove the stem cells, and the remaining blood cells are returned to the patient through the other arm.
- Several sessions of up to six hours are required to harvest, through apheresis, enough stem cells for transplantation

COBE Spectra Apheresis System



Infusion of Stem Cells

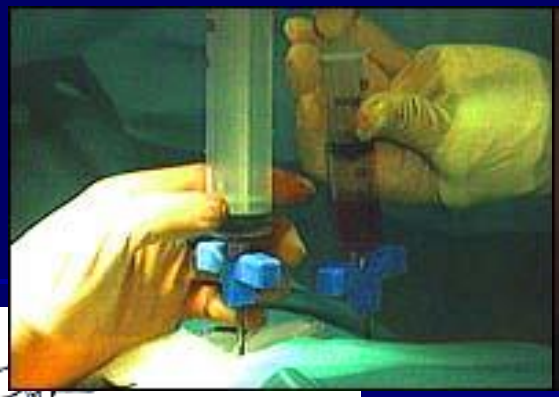
- Stem cells may be infused fresh within a few hours of collection
- May be frozen using dimethyl sulfoxide.
- Umbilical cord blood is obtained from one of the umbilical cord veins and frozen with an anticoagulant and nutrient media

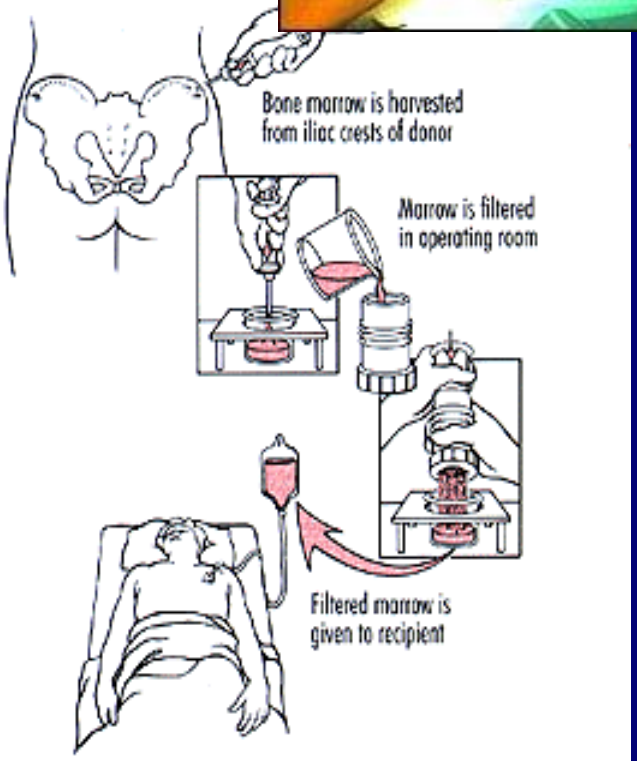
Stem cell processing and infusion

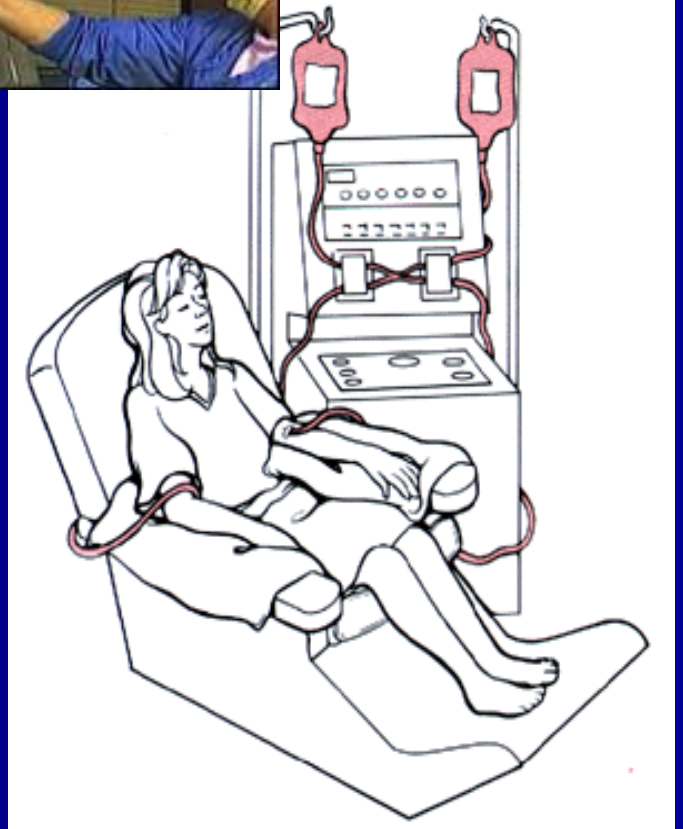
- Infused through a CVL, much like a blood transfusion.
- **Anaphylaxis, volume overload, and a (rare) transient GVHD** are the major potential complications involved.
- Stem cell products that have been cryopreserved contain dimethyl sulfoxide (DMSO) as a preservative and potentially can cause renal failure, in addition to the unpleasant smell and taste(Creamed corn or garlic smell)

Stem Cell Manipulation

- ABO incompatible
  - Removal of isoagglutinins or RBCs
- T-cell depletion
  - Reduce incidence of GVHD
  - Increased graft failure
  - Increased relapse rates
- In vitro purging
  - Removal of tumor cells
  - Positive selection of CD34+ cells




Bone marrow is harvested from iliac crests of donor
Marrow is filtered in operating room
Filtered marrow is given to recipient



Neutropenic Phase

- During this period (2-4 wk), the patient essentially has no effective immune system.
- Healing is poor, and the patient is very susceptible to infection.
- Supportive care and empiric antibiotic therapy are the mainstays of successful passage through this phase.

Recovering from the transplant Engraftment Phase

- Recovery of normal levels cells is called engraftment
- Day 8 - 12
- Neutrophil engraftment important (GCSF) may be given to accelerate the process
- Platelets are the next to return with red cells last.
- Commonly patients require transfusion of red cells and platelets following a transplant.
- Discharge upon neutrophil & platelet engraftment

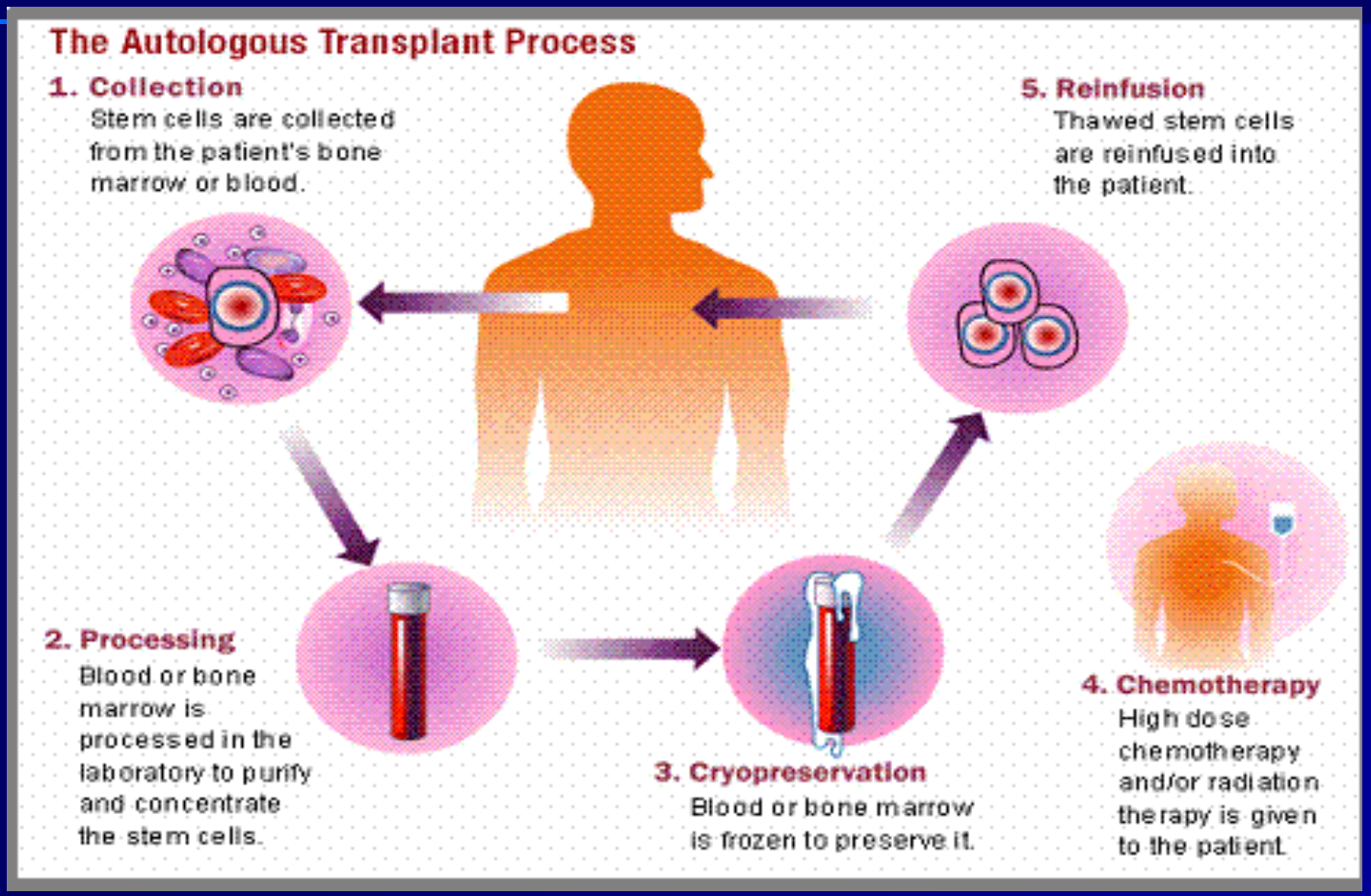
Engraftment Phase

- During this period (several weeks), the healing process begins with resolution of mucositis and other lesions acquired. In addition, fever begins to subside, and infections often begin to clear. The greatest challenges at this time are management of GVHD and prevention of viral infections (especially CMV).

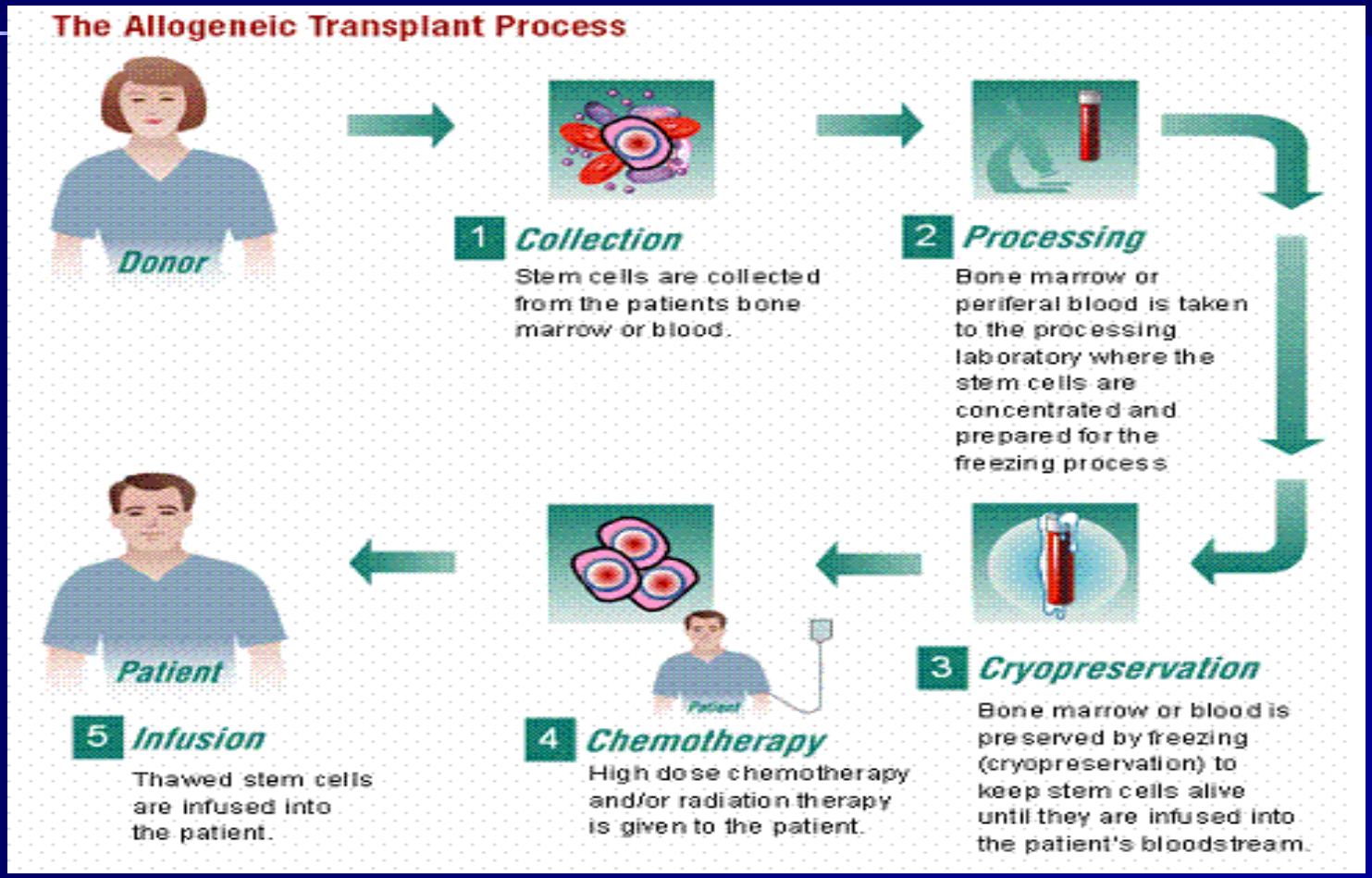
Post-engraftment Phase

- This period lasts for months to years. Hallmarks of this phase include the gradual development of tolerance, weaning off of immunosuppression, management of chronic GVHD, and documentation of immune reconstitution.

Auto Transplant



Allotransplant



Post Stem Cell Transplant Monitoring

- The role of the laboratory in post stem cell transplant monitoring is to provide clinicians with accurate information of the engraftment status by quantitatively determining the proportion of donor and recipient derived cells in the patient post transplant.
- Most laboratories use Short Tandem Repeats (STR's) for this.

Post Stem Cell Transplant Monitoring

- Post stem cell transplant chimerism results are typically reported as % donor chimerism.
- A 100% donor chimera implies complete engraftment.
- A 0% donor chimerism implies no donor engraftment with all other percentages reported as mixed chimerism showing the proportion of donor engraftment.

Complications

- Early
  - Mucositis
  - Sinusoidal obstructive syndrome (VOD)
    - Fluid retention, jaundice, hepatomegaly
  - Transplant related infections
    - Damage to mouth, gut and skin
    - Prolonged neutropenia

Complications

- Early
  - Pancytopenia
    - PRBC and platelet transfusions
    - Broad spectrum antimicrobials
    - Antifungals if prolonged fevers 3-5 days

Graft versus Host Disease (GVHD)

- GVHD sometimes occurs with allogeneic transplantation.
- Lymphocytes from the donor graft attack the cells of the host
- GVHD can usually be treated with steroids or other immunosuppressive agents.
- Acute GVHD occurs before day 100 post-transplant
- Chronic GVHD occurs beyond day 100
- Chronic GVHD can develop months or even years post-transplant

Complications

- Early
  - Graft Rejection
    - Host versus graft
    - Drug injury to marrow
    - Viral infections: CMV, HHV-6 & 8
  - Interstitial Pneumonitis
    - Diffuse alveolar hemorrhage
    - Too few donor stem cells
    - ARDS often caused by CMV

Complications

- Delayed
  - Chronic GVHD
    - Scleroderma or Sjogrens syndrome
    - Bronchiolitis
    - Keratoconjunctivitis
    - Malabsorption
    - Cholestasis
    - Esophageal stricture

Late Complications

- Secondary Tumors
  - Acute leukemias, solid tumors, MDS
  - Months to years after transplant
  - Increased incidence with TBI
- Late Infections
  - Bacterial, viral, fungal
  - Months after transplant
  - Associated with GVHD
  - Need repeat vaccinations
    - Pneumovax, Hep B, Hemophilus influenza b, poliovirus, diphtheria/tetanus, flu

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